	<p>Conclusions: 2D-SWE showed low overall measurement variability, with a minimum of five readings providing equivalent precision to the existing method using 10 samples. Obesity, increasing abdominal wall thickness, sub-capsular measurements and a ROI SD/Speed >0.15 were all associated with increased measurement variability. ROI SD/Speed warrants further evaluation as a quality assessment metric, to allow objective operator assessment of individual 2D-SWE measurement reliability in real-time.</p>

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26 David P Nadebaum
27 Dnadebaum@hotmail.com
28 Department of Cancer Imaging
29 Peter MacCallum Cancer Centre
30 305 Grattan Street
31 Melbourne, Victoria, Australia, 3000.
32 Phone: +61 418 326 616
33 Facsimile: + 613 9076 2599
34

35 **Corresponding author:**
36 **(Post-publication)**

37 Robert N Gibson
38 Robert.gibson@mh.org.au
39 Department of Radiology
40 Royal Melbourne Hospital
41 300 Grattan Street
42 Parkville, Victoria, Australia, 3050.
43 Phone: +613 9342 7255
44 Facsimile: +613 8559 5519
45

46 **Running Title:**
47 Measurement variability of a new 2D-SWE technique.
48
49
50

51 Abstract

52

53 Objectives: A new two-dimensional shear wave elastography (2D-SWE) device has
54 been developed for the non-invasive assessment of liver fibrosis. Guidelines on
55 measurement acquisition parameters are not yet well established for this technique.
56 Our study aimed to assess 2D-SWE measurement variability and to determine the
57 number of measurements required per patient to reliably assess liver stiffness.

58

59 Methods: 2D-SWE was assessed in fifty-five patients with mixed etiology chronic
60 liver disease using the Toshiba Aplio 500 ultrasound system. Ten measurements were
61 obtained per patient by an operator blinded to all preceding readings. Results were
62 analyzed with clinical information obtained from medical records.

63

64 Results: The median IQR/Median ratio for 2D-SWE was 0.131 (q1-q3: 0.089–0.174).
65 Five readings provided an approximation within 0.11m/s or 4.2% of the median
66 velocity of ten measurements. Factors associated with increased measurement
67 variability included BMI ($\rho=0.388$, $p=0.003$), increased skin-to-liver capsule
68 distance ($\rho=0.426$, $p=0.002$) and measurements taken within 1.5cm of the liver
69 capsule ($p<0.001$). Measurements with heterogeneous shear wave profiles (indicated
70 by a ROI SD/Speed ratio >0.15) showed greater deviation from the set's median
71 velocity than those with a ROI SD/Speed ≤ 0.15 (0.42 vs. 0.22m/s, $p=0.001$).

72

73 Conclusions:

74 2D-SWE showed low overall measurement variability, with a minimum of five
75 readings providing equivalent precision to the existing method using 10 samples.

76 Obesity, increasing abdominal wall thickness, sub-capsular measurements and a ROI
77 SD/Speed >0.15 were all associated with increased measurement variability. ROI
78 SD/Speed warrants further evaluation as a quality assessment metric, to allow
79 objective operator assessment of individual 2D-SWE measurement reliability in real-
80 time.

81

82

83

84 **Key words:**

85 Ultrasound, 2D shear wave elastography (2D-SWE), liver, fibrosis, interquartile range
86 (IQR), Obesity

87

88 Introduction

89

90 The management of chronic liver disease relies heavily on the accurate estimation of
91 liver fibrosis, as this is an important prognostic indicator of future clinical outcome.

92 Whilst liver biopsy remains the gold standard for fibrosis assessment, it has a number
93 of inherent limitations which have seen its clinical use decline over recent years. The
94 invasive test is painful, results in hospitalization in 3% of patients and has a
95 procedural mortality rate of approximately 0.01%.^{1,2} The test is also prone to
96 sampling error, with only 1/50,000th of the total liver volume obtained at biopsy.³⁻⁵

97

98 Increasing numbers of non-invasive elastography tools have been developed, which
99 allow clinicians to estimate the severity of a patient's liver fibrosis whilst avoiding the
100 risks of biopsy. These include Transient Elastography (Fibroscan[®]; Echosens,
101 France), Acoustic Radiation Force Impulse (ARFI) imaging (Siemens Medical
102 Solutions, Germany), Magnetic Resonance Elastography (MRE), Aixplorer[®]
103 (Supersonic Imagine, Aix-en-Provence, France) and more recently ElastPQ[®] (Philips
104 Healthcare, USA). Reliability issues however exist for the most widely utilized of
105 these tools, Fibroscan[®] and ARFI, whose performance is variably affected by
106 necroinflammation,^{6,7} obesity,^{8,9} ascites, narrow intercostal spaces,¹⁰ and operator
107 inexperience.⁸

108

109 Shear Wave Elastography utilizing ARFI technology is now sub-classified as point
110 SWE (pSWE) where a very small volume of tissue is stimulated, and two-dimensional
111 (2D) SWE where the elasticity profile of a larger section of tissue is evaluated.¹¹ A
112 new 2D-SWE technique has been developed by Toshiba Medical Systems

Corporation (Tochigi, Japan), which uses shear waves to interrogate the viscoelastic properties of tissues. Ultrasound ‘push pulses’ are used to generate shear waves in the liver, whose propagation is subsequently monitored with ‘tracking pulses’; similar to some other technologies in use. Shear wave arrival times (or ‘wavefronts’) at different locations are plotted, allowing a 2-Dimensional map of shear wave properties within a section of liver to be generated. These shear wave display maps can be viewed in ‘continuous’ mode, however a higher quality ‘single shot’ mode is chosen for quantitative analysis. This involves obtaining a static image of shear wave characteristics within an arc shaped section of liver measuring approximately 35mm in maximal width and 30mm in axial depth. A circular measurement ‘region of interest’ (ROI) of fixed 1cm diameter is subsequently positioned in an area suitable for quantitative assessment (Figure 1). The device automatically calculates the shear wave velocity (meters/second) and Young modulus (kPa) for the chosen ROI; the former recommended by the manufacturer for liver fibrosis quantification. The standard deviation of shear wave velocities within the measurement ROI (ROI SD) is also generated for each individual measurement (Figure 2). Like other ultrasound based elastography tools, 2D-SWE is only able to evaluate areas of liver accessible via a reliable acoustic window (i.e. predominantly the right hepatic lobe). Whilst this introduces a degree sampling error, these technologies are nonetheless able to assess a significantly larger area of liver parenchyma than biopsy.

The technique is novel in the provision of two display maps for the ‘single shot’ acquisition, which provide different visual representations of the liver’s shear wave profile. The first is the ‘Speed Smart Map’ (Figure 1) which provides a color representation of shear wave velocities within a section of liver; similar to that used

138 by Supersonic Shear Imaging (Aix-en-Provence, France). The 'Propagation Map' is
139 however unique to the Toshiba system, and uses contour lines to depict shear wave
140 arrival times at different points in the tissue (Figure 1). These two display maps
141 provide different but complementary information regarding regional shear wave
142 propagation. The additional information provided by the Propagation Map is
143 designed to allow operators to better assess the suitability of 'single shot' acquisitions
144 for quantitative analysis and to optimize ROI positioning.

145
146 The impact of scan acquisition parameters on these technical innovations has not been
147 established, with limited published data currently available for this 2D-SWE
148 technique. Whilst best acquisition practices for related elastography technologies
149 provide a good starting point, there are several unknowns which prevent their direct
150 implementation for 2D-SWE. The aim of our study was therefore to evaluate these
151 technical questions in subjects with diffuse liver disease to assist in the formation of
152 acquisition guidelines. This included analyzing the variability of 2D-SWE
153 measurements obtained within each patient, as well the number of 2D-SWE
154 measurements required per subject to provide a precise assessment of liver elasticity.

155

156

157 **Materials and Methods**

158

159 Subjects:

160

161 Fifty-five patients with diffuse chronic liver disease of mixed etiology were
162 prospectively enrolled in the study. Participants were recruited consecutively, having
163 been clinically referred for the assessment of liver fibrosis. Patients were required to

164 be over 18 years of age for study entry. There were no further exclusion criteria
 165 relating to patient demographics, clinical history or chronic liver disease severity. The
 166 study was approved by the Melbourne Health Research Ethics Committee and all
 167 participants provided informed consent prior to participation.

168

169

170 Patient clinical information:

171

172 Information relating to patient demographics and liver disease etiology was obtained
 173 from medical records. Height and weight measurements were recorded at the time of
 174 2D-SWE for use in Body Mass Index calculations ($BMI = \text{weight (kg)} / \text{height}$
 175 $(\text{meters})^2$). The presence and severity of steatosis was graded according to the level of
 176 echogenicity and beam attenuation observed on B-mode ultrasound.¹² Liver biopsy
 177 results were not available.

178

179

180 Shear Wave Elastography:

181

182 2D-SWE measurements were acquired with the Aplio 500 Platinum Series ultrasound
 183 machine (Toshiba Medical Systems Corporation, Tochigi, Japan) using the PVT-
 184 375BT probe (6-1.9MHz). Measurements were acquired by a single operator, which
 185 included one of three experienced sonographers. All three operators received basic
 186 training in 2D-SWE prior to study commencement, however had significant pSWE
 187 experience having completed in excess of 100 ARFI scans previously. The absence
 188 of ascites was confirmed on B-mode imaging prior to quantitative assessment.

189 Patients were fasted for six hours prior to testing and measurements were acquired in
190 the supine position with the right arm abducted. The scan was performed via an
191 intercostal approach with breathing held in light suspension. Measurements were
192 taken in a single imaging session of less than 10 minutes duration, with the probe
193 firmly applied to achieve acoustic coupling, whilst avoiding compression.
194 Measurements were taken from the right hepatic lobe through a single intercostal
195 space with a good acoustic window. Measurements were obtained in liver
196 parenchyma away from vascular or biliary structures. Samples were taken from non-
197 identical positions within these above parameters. The measurement ROI was
198 positioned in areas of greatest shear wave uniformity; based on the combined and
199 equal review of the Propagation Map and Speed Smart Map. Areas ideal for
200 quantitative assessment were indicated by parallel lines on the Propagation Map and
201 relatively homogeneous color on the Speed Smart Map (Figure 1). Note was made to
202 avoid areas of non-filling on the Speed Smart Map and irregular or fragmented lines
203 on the Propagation Map; indicative of unreliable shear wave characteristics. On the
204 occasion that a 'single shot' acquisition showed no areas suitable for quantitative
205 assessment, the 'single shot' image was reacquired. Whilst fibrosis may not be
206 uniform the assumption is made that the most accurate results are likely to be when
207 there is visible homogeneity within the measurement ROI, as this removes artefactual
208 or technical sources of variation. Ten readings were obtained per patient, one per
209 'single shot' acquisition. Operators were blinded to all individual measurement
210 velocities during the acquisition process via a screen shield. The ratio of ROI SD to
211 the mean shear wave velocity of the corresponding individual measurement (ROI
212 SD/Speed) was calculated. This was assessed as a potential indicator of individual
213 measurement reliability, akin to the use of IQR/Median in assessing the reliability of

214 measurement sets overall. The skin-to-liver capsule distance (SLD) was measured to
215 two decimal points using the picture archiving and communication service (PACS)
216 ruler function (Figure 2). The distance from the liver capsule to ROI center was also
217 manually measured for each individual measurement.

218

219

220

221 Statistical analyses:

222

223 The interquartile range to median ratio (IQR/Median) was assessed for 2D-SWE
224 measurement sets. This indicates the amount of spread between acquired
225 measurements and is a primary indicator of measurement variability in both ARFI and
226 Fibroscan[®].¹³⁻¹⁵ Cronbach's alpha was used to determine the internal consistency of
227 readings and Bland Altman plot for the analysis of optimal measurement number.^{16,17}
228 Measurement distribution was assessed using skewness and kurtosis.¹⁸ The
229 relationship between patient factors and IQR/Median ratios were assessed using
230 Spearman's rank correlation for continuous data and Kruskal-Wallis test for
231 categorical data. The impact of factors affecting the reproducibility of individual
232 measurements (i.e. ROI depth or ROI SD/Speed) were assessed by calculating the
233 deviation of individual 2D-SWE measurements from the set's median velocity of 10
234 readings. Intra-operator and inter-operator reliability were not assessed.

235

236

237 **Results**

238

239 Patient characteristics:

240

241 The cohort consisted of 55 patients, of which 55% were male with an age range of 21
242 to 89 years. Patients with a normal BMI ($<25\text{kg/m}^2$, $n=20$), overweight BMI (25–
243 30kg/m^2 , $n=19$) and obese BMI ($>30\text{kg/m}^2$, $n=16$) were all represented. The most
244 common liver disease etiologies were non-alcoholic fatty liver disease (NAFLD,
245 $n=17$), hepatitis B ($n=16$) and hepatitis C ($n=9$). Patient characteristics are
246 summarized in Table 1.

247

248

249 Measurement variability:

250

251 A large variation in shear wave velocities was observed between individuals (Figure
252 3), with the median overall 2D-SWE of patients being 2.10m/s (q1-q3: $1.81\text{--}2.89\text{m/s}$).

253

254 The median interquartile range (IQR) of 2D-SWE measurement sets was 0.275 (q1-
255 q3: $0.180\text{--}0.575$) and the median IQR/Median ratio was 0.131 (q1-q3: $0.089\text{--}0.174$).

256 There was very high internal consistency between measurements obtained within each
257 patient, with Cronbach's alpha being 0.937 for 5 readings.

258

259 The number of measurements required to adequately approximate the set's median of
260 ten measurements was analyzed. When increasing numbers of measurements were

261 obtained/analyzed, the calculated velocity became predictably closer to the set's

262 overall median of 10 readings (Figure 4). The median of five measurements provided

263 a velocity estimate within 0.11m/s or 4.2% of the set's overall median. The Bland

264 Altman limits of agreement was -0.254 to 0.374m/s for five measurements.

265

266 2D-SWE velocities from each of the 55 measurement sets did not follow a normal
267 distribution, with kurtosis ranging between 3.2 and 5.6 and skewness ranging between
268 1.0 and 1.6. Individual 2D-SWE sets followed a Gamma distribution, with
269 measurements slightly skewed towards higher shear wave velocities.

270

271 Factors affecting measurement variability:

272

273 The association between patient factors and measurement reproducibility was
274 assessed in univariate analyses (Table 1). BMI was the primary factor associated with
275 increased IQR/Median ratios ($\rho=0.388$, $p=0.01$), with overweight and obese patients
276 ($\text{BMI}>25\text{g/m}^2$) demonstrating higher average IQR/Median ratios than those with
277 normal BMI (0.149 vs. 0.112, $p=0.013$). Moderate to severe steatosis on ultrasound,
278 increasing age and a clinical diagnosis of NAFLD were additional factors which
279 showed non-significant trends towards higher IQR/Median ratios (Table 1).

280

281 Skin-to-liver capsule distance (SLD) also showed a moderately strong correlation
282 with IQR/Median ($\rho=0.426$, $p=0.002$, Table 1). Measurements with a SLD $>2\text{cm}$
283 showed considerably greater deviation from the set's median of 10 readings (average
284 deviation = 0.501 vs. 0.268m/s). SLD values were also closely related to BMI
285 ($\rho=0.787$, $p=0.01$).

286

287 The region of interest (ROI) may be positioned at different depths beneath the liver
288 capsule. A greater spread of measurement velocities was observed when the ROI
289 center was positioned within 1.5cm of the liver capsule (Table 2). These subcapsular

measurements showed significantly greater deviation from the set's overall speed (average deviation = 0.39m/s) than measurements taken more deeply in the liver (average deviation = 0.20m/s, $p < 0.001$).

The ROI SD/Speed ratio had a strong relationship with the amount individual measurements deviated from the set's overall median velocity (Table 3). Measurements with a ROI SD/Speed > 0.15 showed low reliability, deviating an average of 0.42m/s from the set's overall median, compared to 0.22m/s for measurements with a ROI SD/Speed ≤ 0.15 ($p = 0.001$). Patient factors associated with increased ROI SD/Speed ratios included increasing BMI ($\rho = 0.499$, $p = 0.003$) and SLD ($\rho = 0.604$, $p < 0.001$). Weaker correlations were also seen with age ($\rho = 0.307$, $p = 0.09$) and the clinical diagnosis of NAFLD ($p = 0.04$). A positive correlation was also observed between ROI SD/Speed and median shear wave velocities ($\rho = 0.496$, $p < 0.001$). The median ROI SD/Speed was also significantly higher amongst subcapsular measurements taken within 1cm from the liver capsule than those taken more deeply in the liver (ROI SD/Speed = 0.169 vs 0.117, $p = 0.002$).

Discussion

The new 2D-SWE technique showed high measurement reproducibility, with a low spread in shear wave velocities (i.e. low IQR/Median) relative to the most widely utilized elastography tools in clinical use.^{7,14,15} Measurement variability, as indicated by IQR/Median ratio, is a powerful predictor of accuracy for both ARFI^{13,14} and Transient Elastography.¹⁵ The low variability of 2D-SWE measurements is therefore encouraging for future accuracy studies.

316

317 The low measurement variability of 2D-SWE also translated into fewer measurements
318 being required to adequately estimate liver stiffness. Acquiring five 2D-SWE
319 measurements yielded a liver stiffness estimate within 5% of the overall median
320 velocity of ten readings. This 5% deviation threshold has been previously used to
321 recommend a minimum of eight measurements for ARFI.¹⁹ Five measurements
322 would therefore appear sufficient using this 2D-SWE technique. The level of
323 deviation is unlikely to have significant impact on the assignment of fibrosis
324 categories, in view of the broad range of median shear wave velocities observed
325 between patients (Figure 3). Given the inherent technical differences between 2D-
326 SWE tools, this measurement number recommendation is specific to the Aplio 500
327 device and may not be directly transferrable to related technologies.

328

329 The low intrinsic measurement variability observed with this 2D-SWE technique is
330 likely attributable to the provision of the ‘Speed Smart Map’ and ‘Propagation Map’.
331 The novel ‘Propagation Map’ is not shared by other conventional elastography
332 methods and provides complementary information which allows operators to better
333 visualize and evaluate regional shear wave propagation characteristics.²⁰ This
334 additional information may enable operators to better assess ‘single shot’ acquisitions,
335 allowing the rejection of acquisitions which are of insufficient quality for quantitative
336 analysis. The display modes also provide guidance for the optimization of ROI
337 positioning; enabling operators to avoid regions with heterogeneous propagation
338 characteristics which may yield aberrant results.

339

Our results likely overestimate 2D-SWE's measurement variability in optimal conditions. Study operators were inexperienced with 2D-SWE at study commencement, which resulted in a number of subcapsular measurements being acquired. These measurements are associated with reduced measurement reproducibility (described below) and their inclusion in composite analyses may have increased the observed IQR/Median ratios. Furthermore, our study had a relatively high prevalence of obesity which may similarly elevate the overall measurement variability observed. The recommendation of a minimum of five measurements is therefore likely conservative and fewer readings may be acceptable under optimal conditions. This is illustrated in Figure 4, in which the exclusion of subcapsular measurements alone reduced the measurement requirement to four. Five readings are however an appropriate recommendation for 'real-world' conditions and amongst similar patient populations.

The observation that 2D-SWE measurement sets do not follow a binomial distribution also suggests that the set's median velocity may be a more robust representation of a patient's overall shear wave velocity than the set's mean.

Obesity:

We found BMI to be the predominant factor affecting measurement variability, with particularly high IQR/Median ratios observed amongst obese patients. A similar association has been previously reported for ARFI^{9,21} and Transient Elastography^{8,9} and our results provide additional evidence to a possible 'class effect' of obesity on

365 ultrasound-based elastography tools in general. Whilst the impact of obesity on the
366 accuracy of this 2D-SWE technique requires assessment, our findings provide early
367 caution that similar reliability issues may be encountered amongst this population
368 subset.
369
370 Obesity's negative impact on ultrasound elastography has been hypothesized to
371 involve ultrasound beam attenuation and degradation from increasing depths of
372 subcutaneous adipose tissue.^{9,21} The skin-to-liver capsule distance (SLD)
373 approximates the amount of subcutaneous adipose tissue traversed by the ultrasound
374 beam and has been found to be a powerful predictor of measurement reliability in
375 ARFI.²² We found SLD to have a stronger correlation with IQR/Median than BMI,
376 which lends weight to this hypothesis. This is further supported by the observation of
377 higher ROI SD/Speed ratios amongst patients with increased SLDs (Table 1),
378 indicating degradation in shear wave quality from central adiposity.
379
380 Whilst we did not formally control for probe pressure in this study, we feel this is
381 unlikely to be a major determinant of SLD. Drawing from unpublished results from
382 our own group looking at 943 patients tested with ARFI by multiple independent
383 operators, we found low inter-operator variability in SLD values obtained within each
384 patient. This suggests any potential difference in operator acquisition technique does
385 not significantly impact on SLD values. The strength of the correlation between BMI
386 and SLD further supports body habitus being the key determinant of SLD, rather than
387 operator technique.
388
389

390 Region of Interest Depth in the Liver:

391

392 We found poorer measurement reproducibility when the center of the ROI was
393 positioned within 1.5cm of the liver capsule. This observation is consistent with
394 existing pSWE studies, which have associated subcapsular readings with artificially
395 elevated fibrosis scores, increased measurement variability and reduced accuracy.^{23,24}

396 ARFI guidelines generally now recommend measurements be taken at least 1cm, and
397 preferably 2cm, from the liver capsule. Our results suggest a similar recommendation

398 should be instituted for the Toshiba system. The phenomenon has been previously

399 attributed to a band of physiologic fibrosis underlying the liver capsule, resulting in

400 disproportionately high shear wave velocities relative to the remaining liver

401 parenchyma. We also speculate that a more important factor is likely to be

402 subcapsular reverberation resulting in regional shear wave degradation. This is

403 suggested by 2D-SWE's Speed Smart Maps, which show an area of heterogeneous

404 shear wave velocity immediately underlying the liver capsule in some patients (Figure

405 1 - 2A). This regional degradation of shear wave profiles is further evidenced by the

406 observation of higher ROI SD/Speed ratios amongst subcapsular measurements

407 (Table 2).

408

409

410 ROI SD/Speed:

411

412 The ROI SD/Speed reflects the variation in shear wave velocities recorded within a

413 measurement ROI on the Speed Smart Map. Measurements with a low ROI SD/Speed

414 reflect regions of liver parenchyma with uniform shear wave profiles, whilst noisy or

415 heterogeneous ROIs translate into higher values. We expected measurements with
416 uniform shear wave profiles would yield the most reliable liver stiffness readings and
417 our results support this hypothesis. We found a strong positive correlation between
418 measurement variability and ROI SD/Speed, with poor measurement consistency
419 observed once the ROI SD/Speed ratio exceeded 0.15.

420
421 The ROI SD/Speed ratio may represent an objective and quantifiable indicator of
422 individual measurement reliability. It has the advantage of being readily assessable
423 during scan acquisition and so has real potential for clinical application. ROI
424 SD/Speed could potentially assist in the optimization of ROI positioning; providing
425 operators with an additional quantifiable indicator of shear wave uniformity in
426 addition to the Speed Smart Map and Propagation Map. The value could potentially
427 alert operators to issues in acquisition technique and may present a means of
428 providing dynamic feedback during operator training or technique modification. ROI
429 SD/Speed ratio may also have utility in stratifying the relative reliability of individual
430 measurements, potentially allowing the rejection of unreliable readings from the final
431 measurement set.

432
433 Future studies are however required to further explore these potential clinical
434 applications. The relationship between ROI SD/Speed and 2D-SWE accuracy also
435 requires assessment, as this will help determine the true utility of ROI SD/Speed as a
436 clinical tool. ROI SD/Speed may also have relevance for Supersonic Shear Imaging
437 (SSI), which also generates a standard deviation of shear wave velocities obtained
438 within each measurement ROI.

439

440

441 Limitations:

442

443 Our study did have limitations. Firstly, the study was a technical paper which aimed
444 to address very specific questions regarding 2D-SWE measurement variability and
445 required measurement number. Liver biopsy is performed in a minority of CLD
446 patients as part of local clinical practice, and a histopathologic correlate was therefore
447 only available for nine patients in the cohort (biopsy performed a median of 5.4 years
448 from 2D-SWE) . Due to the very specific question being addressed, performing a
449 liver biopsy for research purposes was felt unjustified in this study. As a
450 consequence, the accuracy of this new 2D-SWE technology cannot be derived from
451 our results. This will need to be assessed, together with intra-operator / inter-operator
452 reliability in future studies. Nonetheless, our results assist in the formation of
453 acquisition protocols which will facilitate the rigorous and standardized assessment of
454 2D-SWE accuracy and performance in future clinical trials.

455

456 The second limitation was the study's small size; the cohort comprising only 55
457 patients. The study's primary findings were nonetheless all drawn from results of
458 high statistical significance, which underscores the potential clinical relevance of the
459 study's findings.

460

461

462 **Conclusion**

463

464 The new 2D-SWE technique showed low variability between measurements, with a
465 minimum of five readings required to provide a reliable estimation of liver fibrosis.

466 Factors associated with increased measurement variability include increased BMI, a
467 SLD over 2cm and subcapsular measurements. ROI SD/Speed showed a strong
468 relationship with measurement variability and may allow operators to objectively
469 assess the reliability of individual measurements in real-time during the acquisition
470 process.

471

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473

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Accepted Article

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476

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483 collection, data analysis or manuscript preparation.
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485 authors.

486

487

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553 different frequencies in acoustic radiation force impulse (ARFI) elastography: a
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557 **Tables:**

558 Table 1: Demographics and disease characteristics of the patient cohort, with the
 559 median IQR/Median and ROI SD/Speed listed for each patient subset. BMI and skin-
 560 to-liver capsule distance (SLD) showed the strongest associations with both
 561 IQR/Median and ROI SD/Speed.

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Patient Characteristics	No. of patients	IQR/Median, median (q1-q3)	Significance of IQR/Median differences (p value)	ROI SD/Speed, median (q1-q3)	Significance of ROI SD/Speed differences (p value)
Gender					
Male	30	0.137 (0.088-0.269)	0.636	0.155 (0.101-0.208)	0.171
Female	25	0.129 (0.101-0.161)		0.123 (0.081-0.174)	
Age (years)					
<40	13	0.110 (0.102-0.149)	0.624	0.104 (0.077-0.174)	0.09
40-60	28	0.130 (0.104-0.136)		0.132 (0.101-0.174)	
>60	14	0.145 (0.089-0.282)		0.183 (0.157-0.212)	
Body Mass Index (BMI, kg/m²)					
<25	20	0.112 (0.085-0.128)	0.013	0.101 (0.079-0.119)	0.003
25 – 30	19	0.134 (0.074-0.296)		0.153 (0.088-0.178)	
>30	16	0.165 (0.138-0.259)		0.180 (0.154-0.211)	
Liver disease etiology					
NAFLD	17	0.141 (0.129-0.250)	0.145	0.177 (0.151-0.196)	0.043
Hepatitis B	16	0.115 (0.072-0.154)	0.129	0.113 (0.101-0.201)	0.882
Hepatitis C	9	0.118 (0.110-0.269)	0.570	0.122 (0.113-0.222)	0.946
Alcohol	7	0.108 (0.088-0.152)	0.579	0.147 (0.099-0.177)	0.84
Other	12	0.168 (0.119-0.174)	0.757	0.174 (0.125-0.187)	0.105
Hepatosteatosi					
No	26	0.123 (0.089-0.168)	0.543	0.123 (0.099-0.187)	0.351
Mild	15	0.121 (0.088-0.161)		0.153 (0.076-0.184)	

Moderate/Severe	14	0.141 (0.108-0.272)		0.158 (0.141-0.195)	
SLD					
(Set average)					
<1.5cm	12	0.105 (0.070-0.119)	0.002	0.081 (0.073-0.107)	<0.001
1.5 to 2cm	21	0.118 (0.890-0.142)		0.147 (0.099-0.177)	
>2cm	22	0.164 (0.141-0.272)		0.177 (0.152-0.208)	

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571 Table 2: Relationship between measurement depth in the liver (capsule to ROI
 572 distance) and measurement reliability. Sub-capsular measurements showed greater
 573 deviation from the set's overall median velocity and higher ROI SD/Speed ratios.

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Capsule to ROI	Median deviation from the	Median
Distance	set's overall velocity (m/s)	ROI SD/Speed ratio
<1cm	0.578	0.169
1 to 1.5cm	0.284	0.122
1.5 to 2cm	0.191	0.109
>2cm	0.218	0.119

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581 Table 3: Relationship between ROI SD/Speed and measurement reliability. Individual
582 measurements with a ROI SD/Speed ratio >0.15 showed increased deviation from the
583 set's overall median velocity.

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Individual measurement ROI SD/Speed	Number of readings (%)	Average deviation of individual measurements from the set's overall median velocity (m/s)
<0.05	32 (6%)	0.090
0.05 – 0.099	163 (30%)	0.199
0.10 – 0.149	135 (24%)	0.272
0.15 – 0.199	92 (17%)	0.428
≥0.20	128 (23%)	0.413

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588 **Figures:**

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590 Figure 1: Speed Smart Maps (1A, 2A, 3A) show the distribution of shear wave
591 velocities through a section of liver; red areas representing high velocities and
592 blue/green areas low velocities. Propagation Maps (1B, 2B, 3B) show the arrival time
593 contours of shear waves. The region of interest (ROI) is positioned in an area with
594 uniform shear wave characteristics; as indicated by homogeneous color on the Speed
595 Smart Map and parallel contour lines on the Propagation Map.

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598 Figure 2: Screenshot of a 2D-SWE measurement. The shear wave velocity and
599 standard deviation of shear wave velocities within the measurement region of interest
600 (ROI SD) are automatically generated and displayed. Skin-to-liver capsule distance
601 and liver capsule to ROI depth were measured as indicated.

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604 Figure 3: Spread in median shear wave velocities of the cohort's 55 patients. Overall
605 2D-SWE speeds ranged between 1.49 to 5.30m/s, with a median of 2.10m/s.

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608 Figure 4: Closeness in approximation to set's overall median of 10 measurements,
609 according to the number of measurements obtained/analyzed. The graph shows the
610 average deviation +/- SEM. Five measurements yielded a liver stiffness
611 approximation below the 5% deviation threshold (blue). Four measurements were
612 however required if only readings taken >1.5cm deep to the liver capsule were
613 analyzed (red).

Figure 1: Speed Smart Maps (1A, 2A, 3A) show the distribution of shear wave velocities through a section of liver; red areas representing high velocities and blue/green areas low velocities. Propagation Maps (1B, 2B, 3B) show the arrival time contours of shear waves. The region of interest (ROI) is positioned in an area with uniform shear wave characteristics; as indicated by homogeneous color on the Speed Smart Map and parallel contour lines on the Propagation Map.

Figure 2: Screenshot of a 2D-SWE measurement. The shear wave velocity and standard deviation of shear wave velocities within the measurement region of interest (ROI SD) are automatically generated and displayed. Skin-to-liver capsule distance and liver capsule to ROI depth were measured as indicated.

Accepted

Figure 3: Spread in median shear wave velocities of the cohort’s 55 patients. Overall 2D-SWE speeds ranged between 1.49 to 5.30m/s, with a median of 2.10m/s.

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Figure 4: Closeness in approximation to set's overall median of 10 measurements, according to the number of measurements obtained/analyzed. The graph shows the average deviation $\pm$ SEM. Five measurements yielded a liver stiffness approximation below the 5% deviation threshold (blue). Four measurements were however required if only readings taken >1.5 cm deep to the liver capsule were analyzed (red).

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Author/s:

Nadebaum, DP; Nicoll, AJ; Sood, S; Gorelik, A; Gibson, RN

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